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ORIGINAL ARTICLE

Body Composition and Markers of Cardiometabolic Health in Transgender Youth on Gonadotropin-Releasing Hormone Agonists

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Abstract

Purpose: Up to 1.8% of youth identify as transgender; many will be treated with a gonadotropin-releasing hormone agonist (GnRHa). The impact of GnRHa on insulin sensitivity and body composition in transgender youth is understudied. We aimed to evaluate differences in insulin sensitivity and body composition in transgender youth on GnRHa therapy compared with cisgender youth.

Methods: Transgender participants were matched to cisgender participants on age, body mass index, and sex assigned at birth. Transgender males ($n = 9$, ages 10.1–16.0 years) on GnRHa (mean ± standard deviation duration of exposure: 20.9 ± 19.8 months) were compared with cisgender females ($n = 14$, ages 10.6–16.2). Transgender females ($n = 8$, ages 12.6–16.1) on GnRHa (11.3 ± 7 months) were compared with cisgender males ($n = 17$, ages 12.5–15.5). Differences in insulin sensitivity (1/[fasting insulin], homeostatic model of insulin resistance [HOMA-IR]), glycemia (hemoglobin A1C [HbA1c], fasting glucose), and body composition (dual-energy X-ray absorptiometry) were evaluated using a mixed linear regression model.

Results: Transgender males had lower 1/fasting insulin and higher HOMA-IR ($p = 0.031$, $p = 0.01$, respectively), fasting glucose (89 ± 4 vs. 79 ± 13 mg/dL, $p = 0.012$), HbA1c (5.4 ± 0.2 vs. 5.2 ± 0.2%, $p = 0.039$), and percent body fat (36 ± 7 vs. 32 ± 5%, $p = 0.042$) than matched cisgender females. Transgender females had lower 1/fasting insulin and higher HOMA-IR ($p = 0.028$, $p = 0.035$), HbA1c (5.4 ± 0.1% vs. 5.1 ± 0.2%, $p = 0.007$), percent body fat (31 ± 9 vs. 24 ± 10%, $p = 0.002$), and lower percent lean mass (66 ± 8 vs. 74 ± 10%, $p < 0.001$) than matched cisgender males.

Conclusion: Transgender youth on a GnRHa have lower estimated insulin sensitivity and higher glycemic markers and body fat than cisgender controls with similar characteristics. Longitudinal studies are needed to understand the significance of these changes. Clinical Trial.gov ID: NCT02550431.

Keywords: assigned sex; body composition; gender dysphoria; gonadotropin-releasing hormone agonist; insulin resistance; transgender

Introduction

In the United States, 0.7–1.8% of youth identify as transgender (gender identity differs from sex at birth).[1,2] The Endocrine Society recommends initiation of gonadotropin-releasing hormone agonist (GnRHa) therapy at Tanner stage 2 to halt pubertal changes that do not align with the individual's gender identity.[3] There is a rise in the number of patients seeking this treatment at centers around the world.[4]

Transgender youth treated with GnRHa have improved psychosocial functioning[5] and depressive symptoms.[6] Furthermore, young transgender children who

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live openly in their affirmed gender identity and are supported by their families have rates of depression similar to age-matched controls or nontransgender siblings.[7] The Endocrine Society and American Academy of Pediatrics recommend gender-affirmative care.[3,8] However, despite puberty being a time of significant change in metabolism, the impact of pausing puberty on cardiometabolic health is largely unknown.

Prior studies have shown an increase in body fat and decrease in lean mass in transgender adolescents on GnRHa.[9,10] However, participants in one study[10] were older and had a more advanced pubertal stage[9,10] than the Tanner 2 pubertal development recommended for GnRHa initiation in the Endocrine Society guidelines.[3] Therefore, as there are known changes in body composition during puberty[11] some of these changes may have already taken place before GnRHa initiation. Thus, data are lacking on the impact of GnRHa on body composition at younger ages or lower pubertal stages. It is also unknown whether GnRHa treatment affects insulin sensitivity or cardiometabolic health in transgender youth, a treatment known to be associated with increased risk of incident diabetes and coronary heart disease in adults.[12] We hypothesized that GnRHa treatment during puberty would maintain or improve insulin sensitivity and body composition. This study addresses these gaps by evaluating markers of cardiometabolic health in transgender adolescents in the United States on GnRHa therapy, compared with cisgender adolescents.

The aims of this cross-sectional study were to evaluate insulin sensitivity and body composition among adolescent transgender females (assigned male at birth) and transgender males (assigned female at birth) on GnRHa treatment (before initiation of testosterone or estradiol), matched on sex assigned at birth, age, and body mass index (BMI) to cisgender adolescents. Second, we evaluated the association of insulin sensitivity with body fat and duration of GnRH treatment.

Materials and Methods

Participants

Transgender youth who had been on a GnRHa for ≥ 3 months were recruited between 2016 and 2019 from the TRUE Center for Gender Diversity at Children's Hospital Colorado (CHCO). All transgender females and five transgender males were recruited from the same cross-sectional study.[13] An additional four transgender males were recruited from a separate longitudinal study, and data from their baseline visit are included here, when they were on a GnRHa alone. None of the participants were receiving testosterone or estradiol treatment at the time of this study. Youth were excluded if they had significant medical or psychiatric comorbidities (including diabetes or antipsychotic treatment), or were using hormones not prescribed by a physician. The study was approved by the Colorado Multiple Institutional Review Board; consent and assent were obtained from all participants and a guardian.

Data on healthy cisgender controls were obtained from two studies performed at our institution: the RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) study[14] and the Health Influences in Puberty (HIP) study.[15] Inclusion criteria for both RESISTANT[14] and HIP[15] have previously been described. We matched on sex assigned at birth to be able to examine how GnRHa treatment in birth-assigned males and females impacts insulin sensitivity and body composition, relative to birth-assigned male and female controls, respectively, not receiving GnRHa.

Research visit

All transgender participants had a research visit in the morning at the CHCO Clinical Translational Research Center (CTRC) after an overnight fast. Fasted blood samples were drawn. Pubertal staging was performed by a pediatric endocrinologist using the standards of Marshall and Tanner for breast development (using inspection and palpation) or testicular development, and pubic hair.[16,17] Testicular volume was assessed using a Prader orchidometer and assigned a Tanner stage equivalent as follows: Tanner $1 < 4$ mL; Tanner $2 \geq 4$ mL and < 8 mL; Tanner $3 \geq 8$ mL and < 12 mL; Tanner $4 \geq 12$ mL and ≤ 15 mL; Tanner $5 > 15$ mL. Height was measured on a Harpenden stadiometer and weight on a digital electronic scale in light clothing. Height and weight were recorded to the ~ 0.1 cm and kg, respectively. Blood pressure was measured after ~ 5 min of seated rest, with an age- and size-appropriate manual cuff. Weight, height, and blood pressure were each measured twice and averaged. As all participants were < 20 years, pediatric norms for BMI were used (percentile, where 5 to < 85 percentile is normal weight, 85 to < 95 percentile is overweight, and ≥ 95 percentile is obese). The 2000 Centers for Disease Control and Prevention Growth Charts were used to calculate percentiles using sex assigned at birth.[18] Body composition (i.e., fat-free mass and fat mass) was measured by dual-energy X-ray absorptiometry (Discovery A or Hologic Horizon W, Hologic, Marlborough, MA). Participants filled out a

demographic questionnaire, and all study data were managed using REDCap electronic data capture tools hosted at the University of Colorado Anschutz Medical Campus (CU-AMC).[19]

The methods and equipment used for the RESISTANT and HIP studies were the same as used in the transgender participants, including fasted laboratories, anthropomorphics, body composition, and puberty examination unless otherwise noted.

Laboratory assays

Serum/plasma fasted blood samples were assayed for glucose, insulin, lipid panel, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin A1C (HbA1c), leptin, sex hormone-binding globulin (SHBG), luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone. Laboratory assays were performed by the CU-AMC CTRC Core Laboratory and the UC Health Clinical Laboratory, and inter- and intra-assay coefficient of variations (CVs) have previously been described.[13] Insulin sensitivity was estimated by the inverse of the fasting insulin concentration (1/[fasting insulin]) and by the homeostatic model of insulin resistance (HOMA-IR), which are both correlated with insulin sensitivity measured with a hyperinsulinemic euglycemic clamp[20,21]; lower values for 1/fasting insulin and higher values for HOMA-IR indicate worse insulin sensitivity.

Testosterone, estradiol, and SHBG were measured by chemiluminescence (Beckman Coulter, Brea, CA). Testosterone inter- and intra-assay CVs were 5.1% and 2.1%, respectively, and sensitivity 17 ng/dL; estradiol inter- and intra-assay CVs 8.2% and 4.3%, respectively, and sensitivity 10.0 pg/mL; SHBG inter- and intra-assay CVs 5.7% and 3.6%, respectively, and sensitivity 3 nmol/L.

Total cholesterol, triglycerides, and high-density lipoprotein cholesterol were directly measured, and low-density lipoprotein cholesterol was calculated using the Friedewald formula (for units in mg/dL).[22]

Because the AST and ALT for the cisgender participants were measured by a different assay, a correction factor was applied to the transgender participants: corrected AST = (measured AST + 14.374)/0.8334 and corrected ALT = (measured ALT + 10.058)/0.9319. Deming regression was used to build a regression model and determine the correction needed to make the results equivalent using the parameter estimates obtained from the regression.

Statistical analysis

Transgender participants were matched to cisgender controls on age (within a year or less), BMI (within category), and sex assigned at birth; transgender males (assigned female sex at birth, male gender identity) were matched to cisgender females and transgender females (assigned male sex at birth, female gender identity) were matched to cisgender males.

Transgender male participants ($n = 9$, 10.1–16.0 years) were matched to cisgender females ($n = 14$, 10.6–16.2 years) with a range of 1–2 cisgender female matches per transgender male case (1:1 $n = 4$, 1:2 $n = 5$). Transgender female participants ($n = 8$, 12.6–16.1 years) were matched to cisgender males ($n = 17$, 12.5–15.5 years) with a range of 1–3 matches per transgender female case (1:1 $n = 3$, 1:2 $n = 1$, 1:3 $n = 4$).

Tests of differences between transgender and cisgender participants were performed based on mixed linear regression models with a random intercept for the matched set. Compound symmetry was used for the covariance structure, and the restricted maximum-likelihood method was used to estimate the covariance parameters. For group comparisons in which there was more than one cisgender match for the transgender participant, means of the matched set are presented (e.g., if three cisgender males were matched to one transgender female, the mean of outcome for the three cisgender males was obtained; the means and standard deviations (SDs) of the matched set means are reported).

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). p-Values < 0.05 were considered significant. We did not correct for multiple comparisons because all findings in this pilot study are considered exploratory.

Results

Demographics of the overall group are presented in Table 1. Transgender males were treated with a GnRHa for an average (±SD) of 20.9 ± 19.8 months (range 17.5–70.4 months) before study entry. Transgender females were treated with a GnRHa for an average of 11.3 ± 7 months (range 4.7–24.2 months) before study entry. Five (56%) of the transgender males had menarche (average age 12 ± 0.7 years) before starting a GnRHa and eight (57%) of cisgender females were postmenarchal (average age of menarche 12 ± 1.3 years). None of the transgender male participants were having ongoing menses at the time of the study visit.

Table 1. Demographics of Transgender and Cisgender Participants

	Assigned female at birth		Assigned male at birth	
	Transgender males ($n=9$)	Cisgender females ($n=14$)	Transgender females ($n=8$)	Cisgender males ($n=17$)
Age (years)	13.8 ± 1.7	13.9 ± 1.7	13.7 ± 1.2	13.9 ± 0.9
Age at initiation of GnRHa (years)	12.1 ± 1.9	—	12.8 ± 1.3	—
GnRHa duration (months)	20.9 ± 19.8	—	11.3 ± 7	—
Race				
White	6 (67)	10 (71)	7 (88)	13 (76)
Asian	0 (0)	1 (7)	0 (0)	1 (6)
African American	1 (11)	3 (21)	0 (0)	1 (6)
More than one race	1 (11)	0 (0)	1 (12)	0 (0)
Unknown/not reported	1 (11)	0 (0)	0 (0)	2 (12)
Ethnicity				
Hispanic/Latino	4 (44)	4 (29)	4 (50)	3 (18)
Not Hispanic/Latino	5 (56)	9 (64)	4 (50)	13 (76)
Unknown/not reported	0 (0)	1 (7)	0 (0)	1 (6)
Depression	2 (22)	—	3 (38)	—
Anxiety	1 (11)	—	1 (12)	—
Pubic hair Tanner stage				
1	1 (11)	1 (7)	1 (12)	1 (6)
2	0 (0)	0 (0)	3 (38)	5 (29)
3	1 (11)	2 (14)	0 (0)	3 (18)
4	3 (33)	4 (29)	1 (12)	2 (12)
5	2 (22)	1 (7)	1 (12)	1 (6)
Missing	2 (22)	6 (43)	2 (25)	5 (29)
Breast/testicular Tanner stage				
2	1 (11)	1 (7)	5 (63)	7 (41)
3	3 (33)	1 (7)	0 (0)	3 (18)
4	2 (22)	3 (21)	1 (12)	3 (18)
5	2 (22)	9 (64)	2 (25)	4 (24)
Missing	1 (11)	0 (0)	0 (0)	0 (0)
Family history[a]				
Hypertension	5 (63)	6 (75)	5 (63)	9 (75)
Hypercholesterolemia	5 (63)	7 (88)	3 (38)	8 (67)
Type 2 diabetes	4 (50)	7 (64)	1 (13)	4 (33)

Values above represent the entire cohort used and are either presented as mean ± SD or *n* (%).

[a]Family history is given out of total number of reported values (nonmissing). For transgender males, family history was missing for one participant. For cisgender females, family history was missing for hypertension ($n=6$), hypercholesterolemia ($n=6$), type 2 diabetes ($n=3$). Family history was not missing for any transgender female and was missing for 5 cisgender males (all conditions).

GnRHa, gonadotropin-releasing hormone agonist; SD, standard deviation.

Transgender males compared with cisgender females

Markers of cardiometabolic health and hormone concentrations for transgender males are displayed in Table 2 and Figure 1. Transgender males had lower estimated insulin sensitivity than cisgender females, with lower inverse of fasted insulin ($p=0.031$) and higher HOMA-IR ($p=0.010$), higher fasted glucose ($p=0.012$) and higher HbA1c ($p=0.039$). Transgender males also had higher leptin ($p<0.001$) and AST ($p=0.02$) and lower total estradiol ($p=0.014$) than cisgender females. Transgender males had a higher percent body fat (36 ± 7 vs. 32 ± 5%, $p=0.042$) and lower total lean mass (32.3 ± 5.2 vs. 36.4 ± 7.8 kg, $p=0.009$), but not percent lean mass than cisgender females. The mean systolic blood pressure was lower among transgender males compared with cisgender females, although this did not reach statistical significance ($p=0.08$).

Transgender females compared with cisgender males

Markers of cardiometabolic health and hormone concentrations for transgender females are displayed in Table 2 and Figure 1. Transgender females had lower estimated insulin sensitivity than cisgender males, with lower inverse of fasted insulin ($p=0.028$) and higher HOMA-IR ($p=0.035$), as well as higher HbA1c ($p=0.007$), AST ($p=0.007$), and leptin ($p<0.001$) and lower total testosterone ($p<0.001$) than cisgender males. Transgender females had higher percent body fat (31 ± 9 vs. 24 ± 10%, $p=0.002$) and lower percent lean mass (66 ± 8 vs. 74 ± 10%, $p<0.001$) than cisgender

Table 2. Markers of Cardiometabolic Health and Hormone Concentrations

	Assigned female at birth		Assigned male at birth	
	Transgender males ($n=9$)	Cisgender females ($n=14$[a])	Transgender females ($n=8$)	Cisgender males ($n=17$[a])
BMI (percentile)	62 ± 32	67 ± 29	44 ± 39	45 ± 38
Systolic BP (mmHg)	104 ± 13	114 ± 11	97 ± 6	108 ± 7**
Systolic BP (percentile)	41 ± 32	68 ± 24	15 ± 12	52 ± 21***
Diastolic BP (mmHg)	67 ± 5	65 ± 9	65 ± 11	65 ± 3
Diastolic BP (percentile)	59 ± 20	55 ± 25	55 ± 28	57 ± 9
Inverse of fasting insulin (mL/μU)	0.067 ± 0.020	0.103 ± 0.049*	0.076 ± 0.029	0.135 ± 0.049*
HOMA-IR	3.7 ± 1.7	2.3 ± 1.1**	3.5 ± 1.4	2.2 ± 1.3*
Fasting glucose (mg/dL)	89 ± 4	79 ± 13*	88 ± 7	84 ± 5
Hemoglobin A1c (%)	5.4 ± 0.2	5.2 ± 0.2*	5.4 ± 0.1	5.1 ± 0.2**
AST (U/L)	42 ± 11	31 ± 10*	43 ± 9	31 ± 6**
ALT (U/L)	28 ± 13	24 ± 9	34 ± 17	24 ± 6
Total cholesterol (mg/dL)	158 ± 21	152 ± 27	143 ± 16	151 ± 35
Triglycerides (mg/dL)	87 ± 43	89 ± 24	78 ± 28	117 ± 115
HDL (mg/dL)	53 ± 16	48 ± 13	51 ± 6	54 ± 13
LDL (mg/dL)	88 ± 14	86 ± 23	76 ± 14	74 ± 17
Total estradiol (pg/mL)	15 ± 5	58 ± 45*	12 ± 3	14 ± 5
Total testosterone (ng/dL)	29 ± 12	38 ± 12	50 ± 52	231 ± 153***
SHBG (nmol/L)	53 ± 34	47 ± 19	50 ± 24	54 ± 26
Luteinizing hormone (mIU/mL)	1.6 ± 1.8	—	0.8 ± 0.6	—
Follicle stimulating hormone (mIU/mL)	2.7 ± 2.3	—	0.8 ± 0.3	—

Values are given as mean ± SD.
[a]Means of the matched set, *$p<0.05$, **$p\leq0.01$, ***$p\leq0.001$ (p-values represent significance from log-transformed variables when relevant).
BMI, body mass index; BP, blood pressure; HOMA-IR, homeostatic model of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SHBG, sex hormone-binding globulin.

males, and lower systolic blood pressure and systolic blood pressure percentile ($p=0.006$).

Associations

In the pooled population of transgender and cisgender participants, insulin sensitivity assessed by 1/fasting insulin was inversely correlated with percent fat ($r=-0.68$ [95% confidence interval, CI: -0.81 to -0.48], $p<0.0001$) and inversely correlated with BMI percentile ($r=-0.64$ [95% CI: -0.79 to -0.41], $p<0.0001$). Duration of GnRHa treatment did not correlate with insulin sensitivity.

Discussion

In this study, we show that both transgender males and females on GnRHa have lower estimated insulin sensitivity, more evidence of dysglycemia, and higher body fat than age-, assigned sex-, and BMI-matched cisgender controls.

In adult cisgender individuals, there are known effects of having low endogenous sex steroids, either primarily or secondary to exogenous suppression, on body composition and insulin sensitivity. Testosterone deficiency in adult cisgender men is associated with greater visceral fat, insulin resistance, and metabolic syndrome.[23] Blockade of endogenous testosterone with a GnRH agonist or antagonist results in increased body fat, decreased lean mass,[24] and increased risk of incident diabetes.[12,25] It is known that in cisgender adult women, ovariectomy or rapid, severe estradiol deficiency is associated with increased diabetes risk,[23] although less is known about the impact of acute suppression of estradiol on insulin sensitivity.

However, these findings may not be directly applicable to adolescents. Puberty is closely associated with changes in metabolism and body composition, and may be a critical window for development of future cardiometabolic risk. For example, earlier pubertal timing is associated with metabolic syndrome-related derangements,[26] and healthy adolescents develop transient insulin resistance that resolves after puberty is completed.[27] In addition, there are known sex differences in body composition and insulin sensitivity that emerge during puberty; cisgender adolescent girls are known to be more insulin resistant, develop a higher percent body fat, have a greater decrease in habitual levels of physical activity, and have a higher incidence of type 2 diabetes than cisgender boys.[28–30]

Given the negative associations of puberty and early puberty with insulin sensitivity and cardiometabolic risk, we had hypothesized that those on a GnRHa would have better insulin sensitivity than controls.

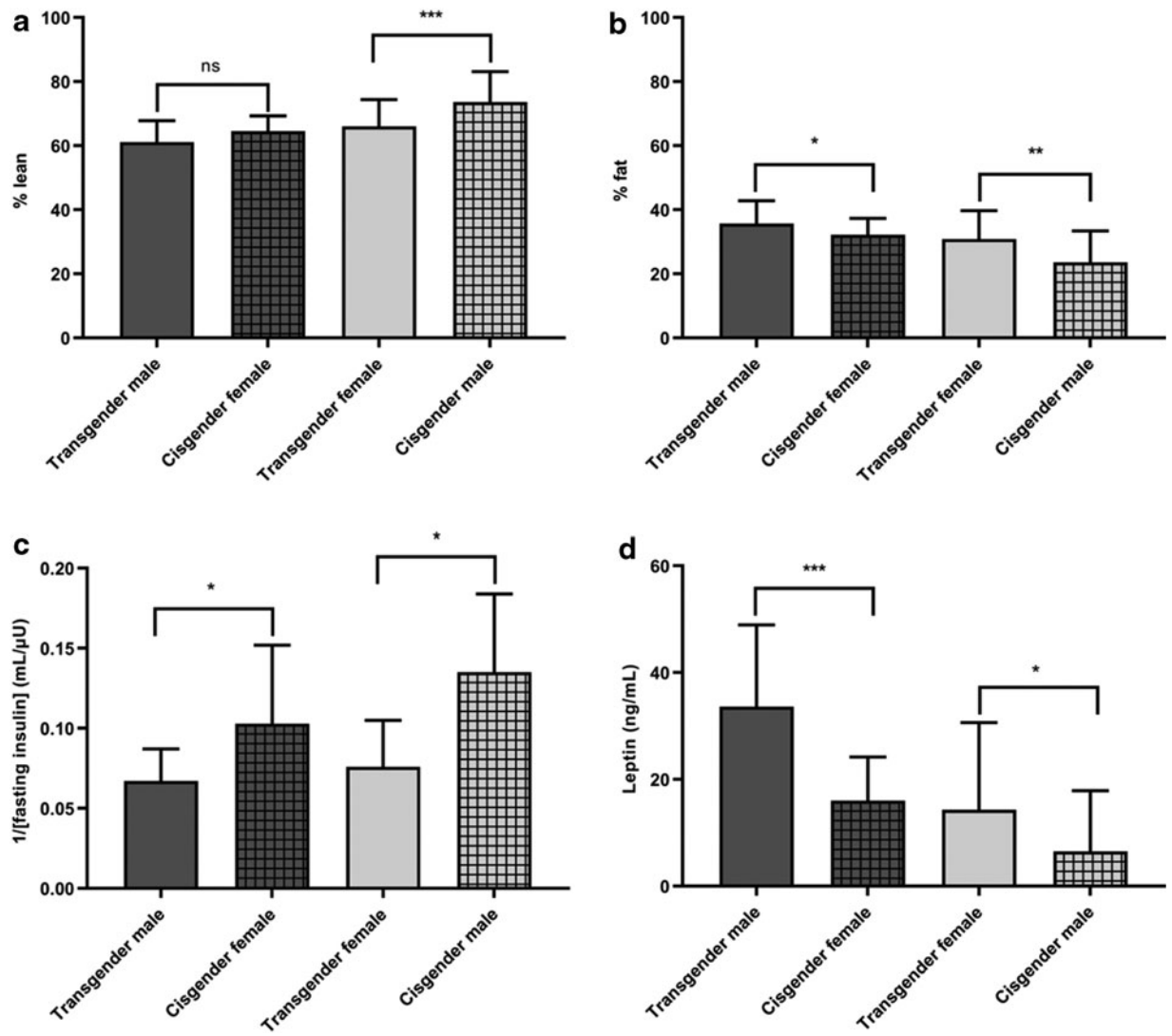

FIG. 1. Body composition **(a,b)**, insulin sensitivity **(c)**, and leptin **(d)** among transgender and cisgender participants. Means and standard deviations are presented; lower 1/[fasting insulin] indicates worse insulin sensitivity, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. ns, not statistically significant.

However, we showed that transgender youth on GnRHa had worse estimated insulin sensitivity than controls. Moreover, since puberty in cisgender individuals leads to greater increases in fat-free mass in males vs. great increases in fat mass in females, we hypothesized that GnRHa would maintain prepubertal body composition. Yet, body composition differences between transgender youth on a GnRHa and cisgender youth were largely in the same direction, regardless of sex assigned at birth. This may suggest that these differences are related to nonsex-specific impacts of GnRHa or to another factor common to transgender individuals. Therefore, our data suggest that suppression of sex steroids during puberty may negatively impact body composition, a finding consistent with prior publications.[9,10]

GnRHa is also used in younger children for the treatment of central precocious puberty (CPP). Youth with CPP treated with a GnRHa show increased fat mass and percent body fat standard deviation score (SDS) and decreased lean tissue mass SDS,[31] although this is not a universal finding.[32] After initiation of GnRHa for CPP, girls who are normal weight have an increase in BMI/BMI *Z*-score but no change in insulin

sensitivity[33,34]; whereas girls who are overweight/obese have no significant change in BMI[33,34] but may have worsening insulin sensitivity.[34] Similar to this study, both of the cited CPP studies used HOMA-IR to estimate insulin sensitivity, as well as other validated estimates.

Despite an increasing number of studies on the impact of testosterone or estradiol on cardiometabolic health in transgender individuals, as reviewed in a recent meta-analysis,[35] the impact of GnRHa treatment on cardiometabolic health remains a vastly understudied area. Similar to longitudinal studies showing transgender adolescents on a GnRHa have an increase in body fat and decrease in lean mass,[9,10] we showed that transgender males and females have a higher body fat percentage than BMI-matched cisgender youth. One study from the Netherlands showed that in the first year of treatment with GnRHa, transgender individuals had increased percent body fat and absolute fat mass and decreased lean mass.[9] However, they also had an increase in BMI, and the changes in body fat were neither adjusted for the changes in BMI, nor compared with a nontransgender population. Another study from the Netherlands evaluated body composition at the start of GnRHa, the start of testosterone or estradiol, and at 22 years of age.[10] Results were adjusted for Tanner stage and BMI at the start of GnRHa treatment. The average age at the start of GnRHa was 14.5 ± 1.8 years for transgender women and 15.3 ± 2 for transgender men (84% had menarche), representing an older and more pubertally advanced population than our population presented here. Percent body fat increased and percent lean mass decreased between the start of GnRHa and the start of testosterone or estradiol.[10] Data are lacking in transgender youth starting GnRHa at younger ages and pubertal stages, and very few comparing results with a matched cisgender population.

The clinical significance of higher HbA1c and/or fasting glucose values that are still within the normal range on cardiometabolic risk among healthy youth is not well understood. It has been suggested that youth should have a fasting plasma glucose < 90 mg/dL, arguing that a mean fasting glucose ~ 90 is of clinical significance.[36] Our group has also shown that obese youth with normal HbA1c ($< 5.7\%$) have glucose excursions above the normal range.[37] Others have shown that the relationship between fasting glucose and cardiovascular disease is J shaped.[38] Since adult transgender individuals on hormone therapy have a higher risk of acute cardiovascular events than cisgender adults,[39] future studies should assess the impact of hormonal interventions as well as physical activity, weight, diet, and other factors, with the goal of reducing future cardiovascular events for this population.

The current cross-sectional study has many strengths. There have been very few carefully performed metabolic studies in transgender youth. Although other studies have evaluated body composition,[9,10] we are not aware of any that have employed a matched group of cisgender controls or that evaluated insulin sensitivity. There are also several limitations to our study. First, our study was cross-sectional, so we do not yet know about changes in insulin sensitivity before versus after GnRHa treatment. Second, the sample size was small. Third, testosterone and estradiol were not measured by mass spectrometry, although these were not our primary outcomes. Fourth, it is known that there are changes in insulin sensitivity during puberty. We were not powered to adjust for pubertal stage in the analyses, but participants were matched on age, a proxy for pubertal stage. In comparisons between transgender youth on a GnRHa and cisgender youth, future studies should evaluate whether it is best to match on Tanner stage or age (would be challenging or impossible to match on both since puberty is being halted in these transgender youth). Fifth, there was a wide range of length of time on a GnRHa. As our study was cross-sectional, it is also possible that other factors might explain the insulin sensitivity differences between transgender and cisgender youth, such as physical activity. We were not able to directly compare or control for physical activity, something that should be accounted for in future studies.

In conclusion, our results show that transgender adolescents on a GnRHa have lower estimated insulin sensitivity and have a metabolically less favorable body composition than cisgender youth with otherwise similar characteristics. Future studies are needed to determine if insulin sensitivity changes or is worse after initiation of GnRHa therapy in transgender youth (and whether timing of initiation impacts outcomes), as well as the subsequent effects of testosterone or estradiol treatment. Longitudinal studies are underway to evaluate these outcomes.

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Author Disclosure Statement

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Abbreviations Used

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BMI = body mass index
BP = blood pressure
CHCO = Children's Hospital Colorado
CPP = central precocious puberty
CTRC = Clinical Translational Research Center
CU-AMC = University of Colorado Anschutz Medical Campus
CV = coefficient of variations
GnRHa = gonadotropin-releasing hormone agonist
HbA1c = hemoglobin A1C
HDL = high-density lipoprotein
HIP = Health Influences in Puberty
HOMA-IR = homeostatic model of insulin resistance
LDL = low-density lipoprotein
RESISTANT = RESistance to InSulin in Type 1 ANd Type 2 diabetes
SD = standard deviation
SDS = standard deviation score
SHBG = sex hormone-binding globulin